BQP Qualification Program Cover Letter

Date: January 16, 2020

Subject: DDT QUALIFICATION SUBMISSION

DDT Type: Biomarker Qualification

ATTN: CDER-Biomarker Qualification Program

C/O CDER Document Room: Upon receipt notify:
CDER-BiomarkerQualificationProgram@fda.hhs.gov

Biomarker DDT Tracking Number: (in bold print), if previously assigned

Check Here	Submission Type
✓	Letter of Intent
	Qualification Plan
	Full Qualification Package
	Update of Above (Check two, this box and one above)
	Other (please specify):

Biomarker Name(s): Oculomotor Index of Gaze to Human Faces

Context of Use: Describe the intended drug development use for the biomarker named above (1 to 2 sentences, see the graphic below for how to write the context of use.)

Diagnostic enrichment biomarker, intended for stratification in clinical trials. It will be used, in conjunction with clinical and demographic characteristics, to obtain a subgroup with reduced DSM-5 ASD-associated heterogeneity.

Contact Information: Complete contact information including name(s), affiliation, mailing address, email address, phone and fax numbers.

1. **James McPartland, Co-chair, Biomarkers Consortium ABC-CT Project Team**
   Associate Professor; Yale Child Study Center
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2. **Linda Brady, Co-chair, Biomarkers Consortium ABC-CT Project Team**
   Director, Division of Neuroscience and Basic Behavioral Science (DNBBS)
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3. **Joseph P. Menetski, Director, Biomarkers Consortium**

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4. **FNIH Biomarkers Consortium, Neuroscience Steering Committee, ABC-CT Project Team**
   FNIH Biomarkers Consortium
   https://fnih.org/what-we-do
   https://fnih.org/what-we-do/biomarkers-consortium/programs

Purpose Statement: Describe the purpose of the submission in 3-5 sentences.

To obtain formal feedback from the FDA regarding an eye-tracking (ET) biomarker (the Oculomotor Index of Gaze to Human Faces) as a diagnostic enrichment biomarker. The ET Oculomotor Index is proposed for use in future clinical trials to select a subgroup of ASD subjects with a potentially shared underlying pathophysiology to enrich samples to enhance signal detection in the testing of novel agents. Elements of the ET Oculomotor Index biomarker are being studied in two major consortia efforts and in a project spearheaded by Janssen R&D, which is why it is being prioritized for submission to the FDA for feedback: 1) this project, the ongoing FNIH Biomarkers Consortium Autism Biomarkers Consortium for Clinical Trials (ABC-CT) study; 2) the Innovative Medicines Initiative (IMI) EU-AIMS Longitudinal European Autism Project (LEAP) study (in Europe); and 3) JAKE (the Janssen Autism Knowledge Engine). The purpose of this submission is to solicit feedback from the FDA regarding the potential viability of the ET Oculomotor Index as a diagnostic enrichment biomarker, the proposed data analytic plan, and next steps for confirmatory studies.

In addition to the Oculomotor Index, these programs are studying other objective measures that may have utility for additional contexts of use, such as discrimination and sensitivity to clinical change, in individuals with ASD. The applicant intends to explore the approach to early evaluation and consideration of multiple potential biomarkers, including both eye-tracking endpoints and EEG endpoints, in conjunction with computer-administered stimuli designed to evoke biological responses.

Submission Statement: Include a statement in the cover letter that: "The physical media submission is virus free with a description of the software (name, version and company) used to check the files for viruses."

The physical media submission is virus free and has been checked for viruses with ESET Endpoint Antivirus software.

Additional Instructions for LOI/QP/FQP[1] submissions: For every electronic submission, a comprehensive table of contents should be submitted containing three or four levels of detail, with the appropriate bookmarks to key referenced sections in the document.

[1] LOI: Letter of Intent; QP: Qualification Plan; FQP: Full Qualification Plan

Biomarker Qualification Letter of Intent (LOI) Content Elements

NOTE TO REQUESTORS: FDA is currently developing its policies for submissions under the 21 Century Cures Act (section 507)[1] and expects to issue guidance to aid in the development of submission based on a decade of reviews, input from public meetings, comments to the docket and collaborative public partnerships. In the interim the Agency has assembled this resource to help requestors. Given the changes to the process as defined in section 507, we expect to see further development of this content over time, with more experience and your input. For additional resources on submission content please see prior Biomarker Qualification Program submissions that we have accepted under section 507 **HERE**. Please also note that certain information contained in submissions will be made publicly available as per section 507, as described in greater detail **HERE**.

Should you have any questions or want to provide feedback on this or other BQP resources, including the content and format of submissions and the transparency provisions under section 507, please contact us at CDER-BiomarkerQualificationProgram@fda.hhs.gov

COMMENTS: The following information will be made publicly available as per section 507, described in greater detail HERE

1. Section 3011 of the 21st Century Cures Act established section 507 of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

Administrative Information

1. **Submission Title**: Oculomotor index of gaze to human faces in autism spectrum disorder (ASD)
   One sentence description of your project. See Abbreviated Biomarker Descriptions in List of FDA Qualified Biomarkers. EXAMPLES:
   - Urinary nephrotoxicity biomarkers as assessed by immunoassays
   - Total Kidney Volume (TKV) as assessed by computerized tomography (CT) scan.

2. **Requesting Organization:**
   FNIH Biomarkers Consortium, Neuroscience Steering Committee, ABC-CT Project Team
   FNIH Biomarkers Consortium
   https://fnih.org/what-we-do
   https://fnih.org/what-we-do/biomarkers-consortium/programs

   1. Primary contact:
      James McPartland, Co-chair, Biomarkers Consortium ABC-CT Project Team
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      james.mcpartland@yale.edu

   2. Alternate contacts:
      Linda Brady, Co-chair, Biomarkers Consortium ABC-CT Project Team
      Director, Division of Neuroscience and Basic Behavioral Science (DNBBS)
      6001 Executive Boulevard, Room 7204/MSC 9645, Bethesda, MD 20892
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      Foundation for the National Institutes of Health
      11400 Rockville Pike Suite 600 North Bethesda MD 20852
      (301) 594-6596
      jmenetski@fnih.org

3. **Submission Dates:**
   Initial submission: October 1, 2019
   Resubmission: January 16, 2020

Drug Development Need Statement

Describe the drug development need that the biomarker is intended to address, including (if applicable) the proposed benefit over currently used biomarkers for similar context of uses (COUs).

There are no FDA-approved drugs designed to reduce the core symptoms of autism spectrum disorder (ASD), which include deficits in social communication and presence of repetitive behaviors. Trials of novel

agents in ASD have been difficult to interpret based on a variety of factors, including the wide heterogeneity in the spectrum of individuals who meet DSM-5 ASD diagnostic criteria and a high placebo response (due to expectation bias and other factors). Controlling for clinical variables, such as sex, age, IQ and severity of core symptoms, has had limited utility in reducing the variability observed in clinical trials. A quantitative diagnostic enrichment biomarker could allow for the selection of a subgroup of ASD subjects with a potentially shared underlying pathophysiology to enhance signal detection in the testing of novel agents in ASD clinical trials.

Biomarker Information and Interpretation

Please provide high level descriptions here and more detailed descriptions in the analytical and the clinical considerations sections.

1. **Biomarker name:** abbreviated short name for biomarker, or names if multiple, AND identify each biomarker type (molecular, histologic, radiographic, or physiologic characteristics according to BEST Glossary). For molecular biomarkers, please provide a unique molecular ID e.g. from UniProt (http://uniprot.org/), HUGO Gene Nomenclature Committee (http://genenames.org), Protein Data Bank (http://rcsb.org/pdb/home/home.do), or Enzyme Commission (http://enzyme.expasy.org).

   EXAMPLES: 25 mRNA gene expression profile/signature; cardiac Troponins T (cTnT) and I (cTnI); Total Kidney Volume (TKV) (please note detection method or algorithm is not a part of the biomarker name). For more examples see the "Qualified Biomarker" column on the FDA List of Qualified Biomarkers website.

   Oculomotor Index of Gaze to Human Faces ("Oculomotor Index")

2. **Analytical methods:** name and briefly describe analytical methods used in raw measurement(s) of the biomarker(s). EXAMPLE: enzyme-linked immunosorbent assay (ELISA) with chromogenic reporters, volumetric analysis of brain magnetic resonance images (MRIs). Include all elements counted/measured/identified and indicate whether measurement is a manual read or a component of the analytic.

   Onscreen gaze position data, reflected in percentage of foveation (angling of the eyes to focus on a particular object) to human faces (Face%) relative to total valid foveation time across three assays.

3. **Measurement units and limit(s) of detection:** describe if any.

   Pixels of (x, y) eye coordinates. Pixels on the screen have an equivalent geometric formulation in degrees of visual angle as measured between the observer's eye(s) and the corresponding (x,y) pixel coordinate on the screen relative to the center of the screen. Eye tracking has a spatial accuracy of .25 to .50 visual degrees (9.7 to 19.3 pixels) and a resolution of .05 RMS visual degrees (2 pixels).

4. **Biomarker interpretation and utility**
   Describe the application/conversion of the raw biomarker measurement in order for the biomarker outcomes to be used for the COU and provide the description and derivation of clinical interpretative

criteria used to include:

a. Post-analytical application/conversion of biomarker raw measure to the applied measure: briefly describe how the raw biomarker measurement is used/applied. Describe if the raw measure is used directly or if there is further processing of the raw measurement into a multi-component panel, a scoring system, or alternatively; further manipulation or transformation of the raw biomarker measurement using modeling, simulation, application of formula(e), other algorithms, or combination with other clinical information. Describe how the process is designed, including software. List the elements, inputs and output(s) of the conversion, including a description of units, if applicable.
b. Describe rationale for post-analytical elements used as inputs in application or conversion of the raw biomarker measurement.
c. Clinical Interpretive Criteria: describe the cut-off values, cut-points/thresholds, boundaries/limits or other comparators used in the interpretation of the biomarker measurement or its applied/converted form to draw an actionable conclusion based on the biomarker result.

Biomarker measurement

In the NIH Autism Biomarkers Consortium for Clinical Trials (ABC-CT) study, which is the reference study for this LOI, foveation was recorded from participants with ASD and their typically developing (TD) peers using an SR Eyelink 1000 Plus eye tracker. Participants sat 65cm from a monitor upon which images and videos comprising the ET assays were presented. These assays were brief (two sessions lasting less than 15 minutes each, conducted over two days) and well-tolerated by participants. Assays entailed passive viewing of stimuli. Eye-tracking data were processed using custom software written in MATLAB™ (*MATLAB version 9.3 (Release R2017b)*, 2017), which performed standard operations, including blink detection, outlier detection, eye-tracking calibration and recalibration, measurements of experimental error, and region-of-interest analysis (Duchowski, 2007; Holmqvist et al., 2011; Shic, 2008). Time varying patterns of foveation were recorded and processed at 500 Hz. Static and dynamic region-of-interest images (focused on heads of characters in scenes, with the regions dominated by the face) were used to analyze the data from three assays: Activity Monitoring (videos and images of two adults engaged in a shared play activity), Social Interactive Scenes (silent dynamic videos of two children playing), and Static Social Scenes (naturalistic, static photographs of adults and/or children accompanied by a soundtrack). Primary dependent variables from individual ET assays contributing to the Oculomotor Index were computed as the proportion of foveation time at human faces relative to foveation at any location on the screen (range: 0-100%).

Trials were marked as valid if there was more than 50% onscreen foveation time during the trial and calibration uncertainty less than 2.5 degrees. Experimental paradigms were considered valid if they contained 25% or more valid trials. The Oculomotor Index was calculated by averaging the percentage of time spent foveating to faces relative to total screen foveation time (Face%) from the three experimental paradigms. If any of the three experimental paradigms was invalid for a participant the entire Oculomotor Index was considered invalid. Equal weighting for the contribution of experimental paradigms to the Oculomotor Index was based on exploratory principal component analyses conducted during the Feasibility Study prior to the ABC-CT main study.

Context of Use Statement (500 characters)

The proposed context of use (COU) statement is complementary to the drug development need statement. Please note that we qualify biomarkers as tools to aid in drug development. While biomarkers may be used for other purposes (e.g., to aid in clinical decision making), COUs that do not address a specified drug development use are outside the scope of the program.

The COU statement may evolve over time based on the information presented in submissions supporting the biomarker's COU and the recommendations made by FDA. However, it should be consistent and worded identically throughout the given version of the submission document. Describing the COU statement early defines the type of information needed in support of qualification for the proposed approach. Although the eventual scope of the project may span over multiple COUs, only a single COU should be initially articulated for a given biomarker qualification submission. Recommended structures of the COU statement are provide below:

BEST biomarker category to **drug development use.**

Or

BEST biomarker category that action, i.e., selects or enriches or indicates or identifies purpose of intervention, e.g., severity, toxicity, susceptibility, disease progression or pharmacodynamic response of target populations, e.g., disease name/stage, patients responsive to treatment in type of study, e.g., early phase trials

EXAMPLES:

A. PD/response biomarker that measures Crohn's Disease (CD) activity used as a co-primary endpoint in CD clinical trials in conjunction with an accepted assessment of patient reported symptoms.

B. Susceptibility/risk biomarker that indicates the potential for individuals to develop symptomatic Type 1 Diabetes (T1D) to study interventions intended to prevent the onset of T1D.

Additional examples of COU statements are available on the Biomarker Qualification Submissions and the Qualified Biomarkers web pages. If assistance in identification of the most appropriate biomarker category is needed, a requestor may contact the Biomarker Qualification Program at CDER-BiomarkerQualificationProgram@fda.hhs.gov.

Diagnostic enrichment biomarker, intended for stratification in clinical trials. It will be used, in conjunction with clinical and demographic characteristics, to obtain a subgroup with reduced DSM-5 ASD-associated heterogeneity.

Analytical Considerations

Please provide the following information (if applicable or available):

- General description of what aspect of the biomarker is being measured and by what method (e.g., lesion

number or specific measure of organ size by imaging, serum level of an analyte, change in the biomarker level relative to a reference such as baseline).

- If this biomarker involves an index/scoring system, please provide information about the elements and weighting of the elements. Include a rational for how the index/scoring system was developed.
- Brief description of sample source, matrix (base material and any additives), stability and composition of biomarker.
- Description of pre-analytical factors and quality assurance/quality control (QA/QC) plans to preserve specimen integrity: a standard operating procedure (SOP) for sample collection including timing and location that sample will be collected from, storage *and* test/assay methodology; reference or control samples.
- Analytical validation plan: description of measurement tool and device calibrations, validation study design with statistical analysis plan (SAP) or performance data (e.g. sensitivity, specificity, accuracy, and/or precision of the assay or method).
- Once the SOP and analytical validation plan is finalized, describe how you will use this process to validate the final version of the measurement tool.
- Additional considerations for imaging biomarkers:
  - How has the method for image acquisition, analysis, and integration of the data been optimized?
  - Does data currently exist to support the proposed cut-off point(s), if imaging results are not reported as a continuous variable?
  - Provide the name and version of the software package to be used for image acquisition and analysis.
  - Description of any software or algorithm used to delineate or segment any physiological structure (i.e. a volume of an organ, a sub-section of an organ, or a size of a vein or opening etc.)
  - Describe any interpretation or transformation of the image data that will be conducted to measure, define, or represent the biomarker in question
  - Provide information on inter-operator and intra-operator variability.

Biomarker description

Atypical activity in brain circuitry in ASD, relative to TD, is reflected in reduced foveation to people. The Oculomotor Index was developed to quantify visual attention to human faces across three assays in an ET biomarker battery: Activity Monitoring (videos and images of two adults engaged in a shared play activity), Social Interactive Scenes (silent videos of two school-age children playing cooperatively or in parallel), and Static Social Scenes (naturalistic, static photographs of adults and/or children accompanied by a soundtrack). A composite was selected (versus metrics derived for individual assays) to capture interrelationships among multiple dependent variables and to reduce measurement error and context effects specific to any single ET assay. This allows us to measure a latent construct that may underlie performance differences both within and between groups. Lower Oculomotor Index scores reflect diminished attentional prioritization for human faces.

A standard operating procedure (SOP) for sample collection, storage and test/assay methodology

ABC-CT ET Standard Operating Procedures are available upon request.

Analytical validation plan

Prior to commencement of the ABC-CT main study, the Oculomotor Index was designated as the primary

ET variable to be assessed for suitability as a biomarker. First, core viability was assessed in terms of (i) successful acquisition across demographic/clinical characteristics, (ii) consistency across study sites, (iii) distributional properties (e.g., absence of severe non-normality, skew, zero-inflation; sufficient variability to show correlations with clinical factors or subgroup differences), (iv) test-retest reliability, and (v) construct validity (the assay elicits a preference for faces as compared to other regions in TD children). Second, we performed a set of tailored analyses to compare the ASD and TD distributions to determine the suitability of the Oculomotor Index for COUs as a discrimination or stratification (diagnostic enrichment) biomarker. Specifically, we used a combination of histograms, descriptive statistics, general linear models, and ROC/sensitivity/specificity curves to look for (i) significant mean differences between ASD and TD groups, (ii) regions of substantial non-overlap (or very different probability concentrations) between the ASD and TD distributions and (iii) multi-modality (indicating a natural separation into subgroups within the ASD group). While the interim analyses showed highly significant mean differences in Oculomotor Index between the ASD and TD groups, the ranges of the distributions had considerable overlap, suggesting that the measure will not function well as a pure discrimination biomarker. Moreover, there was no evidence of multimodality in the distribution of the Oculomotor Index within the ASD group. However, there was a region of non-overlap in the lower tail of the distribution, suggesting that the measure could be used for stratification by identifying a threshold below which the majority of the participants belong to the ASD group. Conceptually, the idea is that this subset might be the result of a distinct underlying neural mechanism within ASD and thereby represent a viable biological target for drug interventions or that it in some other way represents a clinically distinct version of the disorder, thus providing a more homogeneous subgroup for trial enrichment. Mathematically, the goal is to identify the minimum cutoff such that the specificity is above an acceptable threshold for trials and/or the first point at which the reduction in specificity becomes statistically significant. The attached Analysis Plan describes the methods we will use to verify the above findings in the full ABC-CT sample, obtain more precise estimates of the stratification threshold (either overall or as a function of demographic and clinical covariates), and provide a detailed characterization of the ASD subgroup that is outside the normative TD range for the Oculomotor Index.

Clinical Considerations

Please provide the following information (if applicable or available):

- Describe how the biomarker measurement is used to inform drug development. Please provide a decision tree to guide how the biomarker information would be used in drug development or a clinical trial.
- Describe patient population or drug development setting in which the biomarker will be used.
- Clinical validation: provide information to support biological and clinical relevance of the biomarker as applied in the COU:
    - Describe how normal or other reference values are established, provide study design(s), analytical plan, etc.
- Benefits and Risks of applying the biomarker in drug development or a clinical trial.
- Describe any current knowledge gaps, limitations and assumptions in applying the biomarker in drug development or a clinical trial.

At the time of this submission, ABC-CT study data collection has concluded, and final analyses are ongoing. Data presented here are from interim analyses (described in the attached Analysis Plan) including partial data from Time 1 (Baseline) and Time 2 (6 weeks). Final analyses, which commenced at the conclusion of Time 3 (24 weeks) data collection, will address clinical decision making. The intention is to use our complete data set to obtain preliminary estimates of the cutoff score on the Oculomotor Index (or a series of scores based on covariates such as age or gender). A subsequent confirmation study, with a larger TD sample, would be required to replicate the findings and provide more precise estimates of the threshold(s), which could then be used to guide inclusion criteria for future clinical trials. Our objective is to utilize FDA written feedback solicited from this LOI and discussion to inform this process.

Clinical Validation

To be determined with complete dataset.

Benefits and Risks of Applying Clinical Decision Tool

To be determined with complete dataset.

Describe Knowledge Gaps, Limitations and Assumptions

To be determined with complete dataset.

Supporting Information

For example (if applicable or available):

- Provide underlying biological process or supporting evidence of association of the biological process with the biomarker.
- Summary of existing preclinical or clinical data to support the biomarker in its COU (e.g., summaries of literature findings, previously conducted studies).
- Summary of any planned studies to support the biomarker and COU. How will these studies address any current knowledge gaps?
- Please describe alternative comparator, current standard(s), or approaches.

Biological rationale

Convergent evidence from humans, non-human primates, and vertebrate mammals indicates that visual attention to faces is highly conserved across evolution and plays a critical role in social communication. Extant research reveals a distinct and consistent pattern of attention to faces, eyes, and conspecifics in typical development. This bias to orient to and focus on faces is dependent on specific brain regions important for social information processing, including the superior colliculus, amygdala and the superior temporal sulcus, and damage or deactivation of these areas is associated with reduced orienting to people (Campbell, Heywood, Cowey, Regard, & Landis, 1990; Jure, 2019; Pitcher, Duchaine, & Walsh, 2014; Spezio, Huang, Castelli, & Adolphs, 2007). Neuroimaging studies indicate that these brain regions are implicated in autism, and ET enables quantification of their integrity in a non-invasive and tolerable fashion. For example, administration of intranasal oxytocin to adults with ASD was shown to promote prosocial behaviors, foveation to human faces (Andari et al., 2010; Guastella, Mitchell, & Dadds, 2008), and modulate brain activity in amygdala and temporal cortex (Andari, Richard, Leboyer, & Sirigu, 2016).

A meta-analysis of 122 eye-tracking studies showed that individuals with ASD display reduced visual attention to eyes and face regions of human images or videos compared to controls (Frazier et al., 2017).

Across multiple studies of individuals with ASD, attention patterns towards faces associate with severity of autism symptoms and social-communication (Chawarska, Macari, & Shic, 2012; Jones, Carr, & Klin, 2008; Klin, Jones, Schultz, Volkmar, & Cohen, 2002; Shic, Bradshaw, Klin, Scassellati, & Chawarska, 2011) Murias et al., 2018). The Oculomotor Index can be interpreted as an index of severity, with lower scores indicating greater ASD neurobehavioral pathology. However, while group differences are consistently found, there is overlap among individuals, and the nature of the relationship between the visual attention to faces and the clinical phenotype is complex. We will use the full ABC-CT cohort to provide a detailed multivariate profile of the subset of ASD subjects with atypical Oculomotor Index Scores and use this to help identify a cut-point that will define a clinically more homogenous subgroup.

Summary of existing preclinical or clinical data

Eye-tracking indices are a promising biomarker for ASD and have been the focus of > 200 papers in the peer-reviewed literature. ET has been demonstrated to have high potential as a tractable biomarker indexing attention to conspecifics in ASD because it does not require a high level of examiner training and does not require task response, rendering it applicable across multiple testing contexts and for individuals spanning a wide range of age and levels of intellectual ability. Recent research suggests that eye tracking may be highly relevant to both behavioral (Bradshaw et al., 2019; Murias et al., 2018) and pharmacological (Umbricht et al., 2017) intervention research. Foveation patterns to faces in children with ASD associate with common clinical outcome measures (Murias et al., 2018), track changes in language during behavioral intervention (Bradshaw et al., 2019), and reveal increased attentional sensitivity to biological motion in a pharmacological intervention (Umbricht et al., 2017). The three paradigms involved in the composite Oculomotor Index variable were chosen based on successful prior application in these and other ET studies in ASD.

Previous literature in Activity Monitoring shows compromised foveation to the activities of others in toddlers (Shic et al., 2011) and to faces of others in toddlers and adults with ASD (Foster et al., 2016; Shic et al., 2014, 2011). Similarly, in tasks that examine free-viewing of dynamic, social interactions, such as the Social Interactive Scenes task, the TD group shows higher visual prioritization to the eyes and face than ASD (Chevallier et al., 2015; Frazier et al., 2017; Speer, Cook, McMahon, & Clark, 2007). Visual search tasks have demonstrated that infants as young as 5 months orient to faces in an array of non-social objects, more than would be expected by chance, and 6-month-olds and TD adults alike maintain their attention to faces more than toward other objects (Di Giorgio, Turati, Altoè, & Simion, 2012; Gliga, Elsabbagh, Andravizou, & Johnson, 2009). The Static Scenes paradigm extends traditional visual search tasks by providing complex naturalistic scenery, typically photos of real-world situations with carefully arranged interior content such as placement of people versus objects and other non-social features (e.g. landscape). Results have shown between-group differences in atypical foveation following viewing of static scenes (Freeth, Chapman, Ropar, & Mitchell, 2009), as well as atypical orienting to people (Riby & Hancock, 2009) during viewing of static images, in individuals with ASD relative to TD individuals.

The Oculomotor Index was acquired on 222 (out of 225) 6-11 year old children with TD (*n*=64) and ASD (*n*=158) in the ABC-CT interim sample; thus 99% of the interim sample (100% TD and 98% ASD) provided a valid Oculomotor Index. Test-retest-reliability was also excellent: across two measurements separated by 6 weeks, we found an overall ICC of .83 overall with values of .82 in the TD group and .79 in ASD group. The Oculomotor Index was significantly lower [*F*(1,220)=51.5, *p*<.01] in the ASD group (*M*=.214; *SD*=.070)

than in the TD group (*M*=.290; *SD*=.073). In an ROC analysis, the Area under the Curve was moderately, although not extremely, high at .78 (95% CI: .72-85), suggesting that, while the Oculomotor Index does not fully separate the groups, it should be possible to identify a substantial subset with high specificity.

Use of a composite Oculomotor Index was designated prior to main study data collection. Given conceptual overlap among contributing assays with variation in task characteristics across assays (e.g., presence of language, dynamism), the composite Oculomotor Index score was deemed a more robust measure of the construct across samples. For transparency, we provide the metrics for the same dependent variable in the three contributing assays: Activity Monitoring [*F*(1,223)=85.54, *p*<.01; Area under Curve=.83 (95% CI: .77-88, *p*<.01); ICC=.85 (TD=.83, ASD=.79)], Social Interactive [*F*(1,221)=37.2, *p*<.01; Area under Curve=.78 (95% CI: .70-85, p<.01); ICC=.54 (TD=.13, ASD=.25)], Static Scenes [F(1,219)=11.7, p<.01; Area under Curve=.67 (95% CI: 59-74, *p*=.04); ICC=.53 (TD=.42, ASD=.54)].

Summary of any planned studies to support the biomarker and COU

The ABC-CT was designed to examine the Oculomotor Index in 200 children with ASD and 75 TD children across three time points (T1=Baseline, T2=6 weeks, T3=24 weeks). Analyses in the full sample will be conducted to confirm the core psychometric properties of the Oculomotor Index assessed at interim in terms of: (i) successful acquisition across sites and across key demographic and clinical characteristics, including age, sex, and level of intellectual ability; (ii) appropriate distributional properties; and (iii) adequate test-retest (T1 / T2) reliability and consistency across sites. We will also repeat the analyses comparing the distributions of the Oculomotor Index in ASD and TD participants to confirm its potential as a diagnostic enrichment biomarker, obtain better estimates of stratification thresholds, and provide a detailed characterization of the resulting subgroup(s). These analyses seek evidence for establishing utility in denoting a more mechanistically homogeneous subgroup of individuals with ASD as evidenced by diminished attention towards faces than in other individuals with ASD and not commonly observed in TD subjects. On January 9, 2020, a renewal application for the ABC-CT was submitted that, relevant to the proposed context of use, would support a confirmation study of Oculomotor Index results in 200 children with ASD and 200 children with TD, with comparable demographics and study design to the original ABC-CT sample.

Alternative/comparator/current standard(s) approaches

Given the absence of quantitative biomarkers for the proposed context of use, there are currently no alternative approaches.

Previous Qualification Interactions and Other Approvals (if applicable)

For example:

- Letter of Support (LOS) issued for this biomarker
- Discussion in a Critical Path Innovation Meeting (CPIM)
- Previous FDA Qualification given to this biomarker with DDT Tracking Record Number
- Qualification submissions to any other regulatory agencies with submission number
- Prior or current regulatory submissions to Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), and Center for Devices and Radiological Health (CDRH). Provide 510(k)/PMA Numbers

Letter of Support (LOS) issued for this biomarker on date:

N/A

Discussed in a Critical Path Innovation Meeting (CPIM) on date:

N/A

Previous FDA Qualification given to this biomarker with DDT Tracking Record Number

N/A

Qualification submissions to any other agencies with submission number

The submitters have not submitted to any other agency; however, a collaborating study, the EU-AIMS Consortium (IMI), submitted a request for scientific advice to the EMA in December 2013, Submission #EMEA/H/SAB/045/1/QA/0000/PED (upon receipt of feedback #EMEA/H/SAB/045/1/QA/2014/PED)

Prior or current Regulatory submissions to Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), and Center for Devices and Radiological Health (CDRH)

N/A

Attachments

This section may contain:

- Please provide a list of publications most relevant to this biomarker development proposal.

Attachment: Publications Relevant to Biomarker Development Proposal

- Optional: If this biomarker development effort is part of a longer-term goal, please summarize your long-term objectives.

Attachment: Draft Analysis Plan Outline for Oculomotor Index Letter of Intent

- Optional: If you have other supporting information you would like to provide, please submit as attachment(s).

Attachment: FDA Involvement in Biomarker Development Proposal

Attachment: ABC-CT Interim Analysis Oculomotor Index Experiment and Data

Please note that any information provided as optional attachments will not be publicly posted.

Additional Information & Submission Information:

Please refer to the Resources for Biomarker Requestors for the mailing address and other important submission-related instructions. For more about Biomarker Qualification see our program's Home Page. If you have any questions about submission procedures, please contact via email; CDER-BiomarkerQualificationProgram@fda.hhs.gov.

Publications Relevant to Biomarker Development Proposal

Andari, E., Duhamel, J.-R., Zalla, T., Herbrecht, E., Leboyer, M., & Sirigu, A. (2010). Promoting social behavior with oxytocin in high-functioning autism spectrum disorders. *Proceedings of the National Academy of Sciences*, *107*(9), 4389–4394. doi: 10.1073/pnas.0910249107

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DRAFT Analysis Plan Outline for Oculomotor Index Letter of Intent

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Introduction: The Oculomotor Index of Gaze to Human Faces, defined as the average percentage of time spent foveating upon human faces across three experimental eye-tracking (ET) paradigms (Activity Monitoring, Social Interactive Scenes and Static Social Scenes) was specified as the primary eye-tracking measure of the Autism Biomarkers Consortium for Clinical Trials (ABC-CT) prior to commencement of the main study. As described in our Letter of Intent, it performed well in terms of core psychometric properties in the ABC-CT interim analyses, including high rates of valid data acquisition (≥ 98% in ASD; 100% in TD), consistency across sites, appropriate distributional properties, high test-retest reliability (ICC's of .84 in ASD and .83 in TD, respectively) and good construct validity. It was therefore designated for submission to the CDER Biomarker Qualification Program. Here we describe the next stage of planned analyses, focusing our attention narrowly on the aspects related to our selected COU.

Context of Use: One of the main uses of a biomarker is as an enrichment tool, to identify an optimal subgroup for inclusion (or exclusion) from a clinical trial. Determination of a subgroup through stratification may be either unsupervised, meaning the subgroups are determined based on the distributional properties of the measure alone, or supervised, meaning the subgroups are identified with respect to diagnosis or to some other outside referent. We have initially positioned the Oculomotor Index biomarker for a COU as a diagnostic enrichment biomarker intended for stratification in clinical trials to, in conjunction with clinical and demographic characteristics, to obtain a subgroup with reduced DSM-5 ASD-associated heterogeneity. The assessment that the Oculomotor Index has potential as a diagnostic enrichment biomarker is based on a comparison of its distribution in the ASD and TD groups (shown in Figure 1). There is no evidence of clearly separable subgroups (or multimodality) in the ASD distribution, so unsupervised stratification approaches, such as cluster analysis, are unlikely to produce a clinically meaningful partition into ASD subtypes based on the Oculomotor Index alone. However, there is a clear region of minimal to non-overlap (highlighted in purple in Figure 1), with a subset of ASD children showing much lower Oculomotor Index scores than are seen in their TD counterparts, suggesting strong potential for the success of diagnostically supervised stratification. Here we lay out a series of analyses designed to confirm the distributional properties of the biomarker, estimate stratification threshold(s), and pinpoint the optimal use(s) of the biomarker for enrichment purposes.

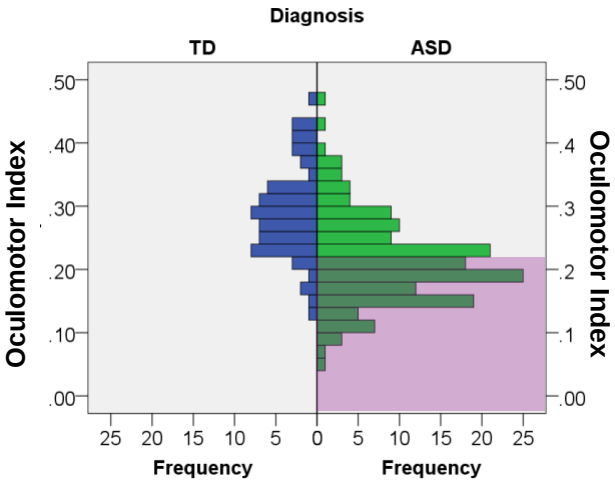


Figure 1. Histogram of Oculomotor Index of Gaze to Human Faces in TD and ASD. Highlighted purple area illustrates a potential subgroup defined by the biomarker.

Distributional Properties and Individual Differences: Using the data from all three time points for the full ABC-CT sample, we will perform a detailed analysis of the distributional properties of the Oculomotor Index biomarker across key subgroups, including checks for non-normality, floor/ceiling effects, outliers, and other influential features. If the distribution of the biomarker varies substantially by

demographic, clinical or experimental characteristics, this would be problematic for development of universal stratification cutoffs, as a particular value would not have consistent interpretations. We will obtain numerical descriptive statistics (e.g., mean, median, standard deviation, coefficient of variation, fraction of values outside the normative range) to assess the consistency of the distribution of the Oculomotor Index across diagnostic status, time, sites and a range of subject characteristics, and will also use side-by-side histograms to graphically compare the shape of the entire distribution in different subgroups and identify the influential features listed above. In addition, we will use GLMMs to model the Oculomotor Index as a function of diagnostic group, along with any demographic and clinical characteristics that would suggest that an adjusted value might improve interpretability. We are specifically interested in the effect of age, as the Oculomotor Index is lower in younger than older typically-developing children in our sample, as depicted in Figure 2. We do not currently apply any algorithmic adjustments such as formulas, modeling, or scoring systems to the biomarker value. As part of the next stage of analyses, we will re-evaluate the biomarker construct with respect to this issue and examine its effects on establishing cut-points or conducting other planned sensitivity analyses.

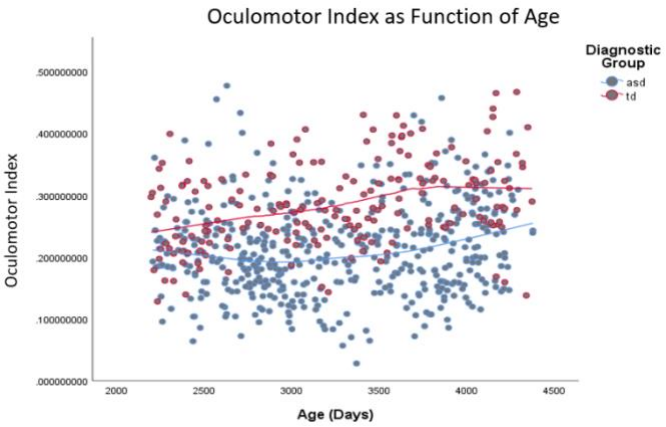


Figure 2. Relationship between age (x-axis) and Oculomotor Index (y-axis) in ASD (blue) and TD (red) samples. Loess fit lines are shown for each group.

Selecting an ASD Subgroup: Standard discrimination cutoffs are chosen to jointly optimize sensitivity and specificity. Our data, instead, suggest a focus on specificity alone, by identifying a cutoff for the Oculomotor Index below which nearly all participants belong to the ASD group. Conceptually the idea is that there might be a distinct underlying neural mechanism within ASD for which this subset would be enriched and might thereby represent a viable biological target for drug interventions, or that it in some other way represents a clinically distinct or more severe version of the disorder, thus providing a more homogeneous subgroup in which to conduct a clinical trial. Our goal will be to identify the cutoff corresponding to the highest Oculomotor Index value (maximizing the available *n* for clinical trials) such that the concentration of ASD subjects is stable and high. Visually, this can be seen by plotting the percentage of subjects above the cutoff who have ASD as a function of cutoff and look for the point at which that percentage begins to drop substantially. Mathematically, this corresponds to finding the maximum cutoff such that the specificity is above an acceptable threshold for trials (to be determined in concert with FDA experts) and/or that the first point at which the reduction in specificity becomes statistically significant. We will use bootstrap methods to get estimates of uncertainty associated with the cutpoints selected via these criteria. While we expect this uncertainty to be relatively high given the small size of the TD sample, this will form the basis for power calculations for future validation studies. We will also look at how this cutpoint varies as a function of other demographic, clinical, and other factors.

Homogeneous Subgroup(s) and Correlations with Clinical Measures: The analysis above is predicated on the idea that the region of non-overlap corresponds to a mechanistically distinct ASD group and that it is therefore possible to select a meaningful cutoff based purely on diagnostic status, using the point at which the number of TD subjects with such low Oculomotor Index values becomes small, without reference to any other factors. However, the mechanistic argument would be strengthened by convergent validity with other clinical measures. Moreover, even if there isn't a neural mechanism that we can identify based on existing data, stratification can be used to great effect by identifying a subgroup of ASD subjects who are more homogeneous with regard to a range of factors.

Thus, in addition to looking at purely diagnostic cutoffs, we will also look for a subset of individuals, based on the Oculomotor Index, that is “different” or “more homogeneous” in terms of clinical measures of social (SRS social communication index of autism traits) or adaptive function (Vineland Adaptive Behavioral Scale Socialization Standard Score and Sub-domain Interpersonal Relationships Score). Thus, we will identify characteristics of the “subgroup” of individuals with Oculomotor Index values that are outside of the TD distribution, both by looking at individual measures and by creating a multivariate profile. We note that analyses examining the relationships between the Oculomotor Index biomarker and clinical measures will not only help us address issues of sample heterogeneity, but will also provide information about sensitivity to clinical change, as we will assess the associations across all three study visits. We will use the cutpoints estimated based on the area of non-overlap between the ASD and TD groups as the starting point for this investigation, but will also perform sensitivity analyses to assess whether the strength of the associations with outside measures/homogeneity of the selected subgroup can be substantially improved by varying the cutpoint.

ET Measurement Issues: Ultimately, a critical component of the Oculomotor Index validation process will be to ensure that the values of the biomarker are consistent across choices of equipment, processing pipelines and implementation (or else to specify constraints on those parameters that will ensure reliable measurement). While the methodological work necessary to carry out a full assessment of the ET measurement performance related to signal to noise and individual trial variability is not the focus of the ABC-CT or this LOI, the necessary extent and specifics can be substantially informed by our current data. That is, based on our proposed exploration of the psychometric properties of the biomarker and further optimization of the COU, we will have a more narrowly focused path to identifying the proper signal property analyses. We note that validation of consistency of a physiological measurement is different than for a biomarker based on a blood or tissue samples, which can be subdivided to perform replication assays. Examples of possible approaches in the context of our ET markers include split-half or block analyses to assess within subject consistency and looking at the variability in Oculomotor Index as a function of the number of (randomly selected) trials included. These approaches would require substantial re-processing work and other methodological issues could only be addressed with additional data. As a caveat, it is also possible that lack of reliability in split-half or block analysis might represent a signal of interest, as these might reflect atypical habituation (i.e., change of the signal over multiple stimulus presentations) or trial-to-trial variability. There are several other preliminary analyses we can perform with our current data that will shed light on these issues. First, for the ABC-CT interim analyses, we considered a subject to have usable data if they had 25% of valid trials within each sub-index comprising the composite. We will perform sensitivity analyses examining the consistency of the biomarker findings, including estimates of stratification thresholds, using different numbers of trials (or other quality cutoffs). Second, we will look at the effects of variability in recording conditions, such as examining small environmental variations within and across our sites. These differences include differences in lighting conditions and room geometry.

FDA Involvement in Biomarker Development Proposal

Submission of this Letter of Intent is to request formal biomarker qualification feedback from the FDA on one of the biomarkers (Oculomotor index of orienting to human faces in autism spectrum disorder) in the Autism Biomarkers Consortium for Clinical Trials (ABC-CT) project. FDA members from Psychiatry Review Division at CDER have been involved in providing feedback on the design and conduct of the project since its inception in June 2015. The ABC-CT project is overseen by the FNIH Biomarkers Consortium (BC) Neuroscience Steering Committee, with a designated Project Team (BC PT) that includes FDA members. During the course of the study, the BC PT has included Peter Como, Silvana Borges, David Millis, and Bernard Fischer. In addition to the BC PT, the FNIH BC Executive Committee, which includes FDA members, Janet Woodcock, Chris Leptak, and Vasum Peiris, has provided ongoing feedback on the ABC-CT biomarker development project (design, feasibility study, and interim analysis) at the quarterly meetings. FDA members of the FNIH BC PT have participated in annual ABC-CT All Investigator Meetings and provided feedback. Chris Leptak attended the face to face BC Neuroscience Steering Committee in October 2017 to present information about the biomarker qualification program and at a recent BC Executive Committee meeting, encouraged the ABC-CT BC PT co-chairs to submit a LOI to the FDA to obtain formal feedback on qualification of the biomarkers.

ABC-CT Biomarker Acquisition

- Oculomotor index
  - ASD: 97-99% across time points
  - TD: 98-100% across time points

Primary ET Biomarker: Oculomotor index

- Oculomotor index of orienting to human faces
  - Foveation to onscreen faces and heads
  - Modulated by amygdala and superior temporal sulcus
  - Reduced foveation to faces in ASD
- Experiments
  - Two classes of videos
  - Images of social interactions
- Prediction
  - Reduced proportion of foveation to faces in ASD

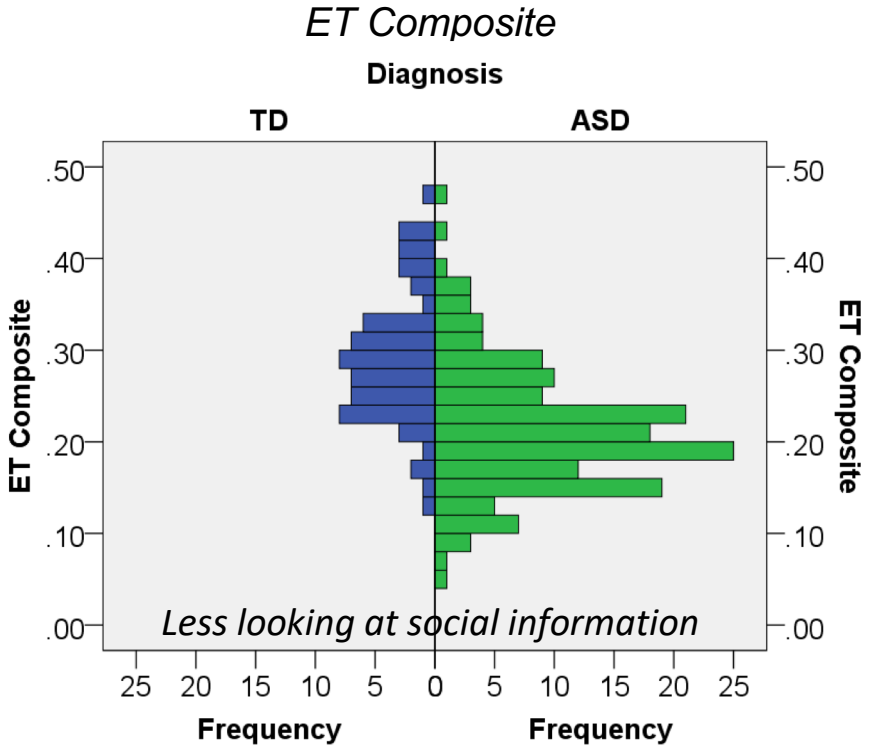
Activity Monitoring

Social Interactive

Static Scenes '

Primary ET Biomarker: Oculomotor index

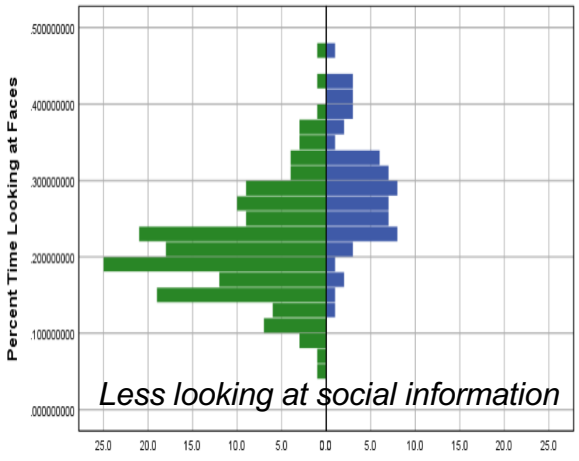
	Whole sample (N=222)	TD (N=64)	ASD (N=158)	Test TD vs ASD	*p*
Mean	.236	.290	.214	F(1,220)=51.5	<.01
SD	.079	.073	.070		



Primary ET Biomarker: Oculomotor index

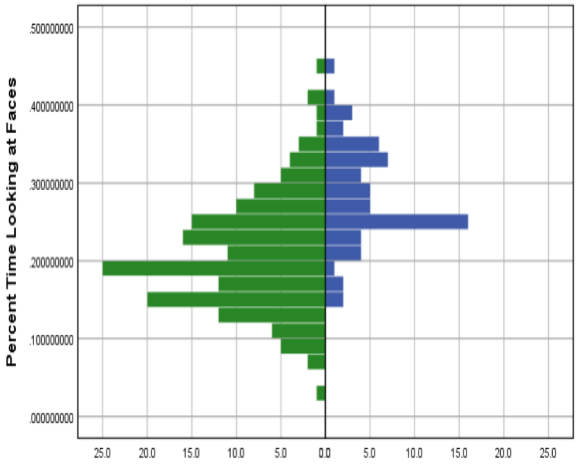
Time 1 (Baseline)	*Time 2 (6 weeks)*	*Time 3 (6 months)*

ASD TD



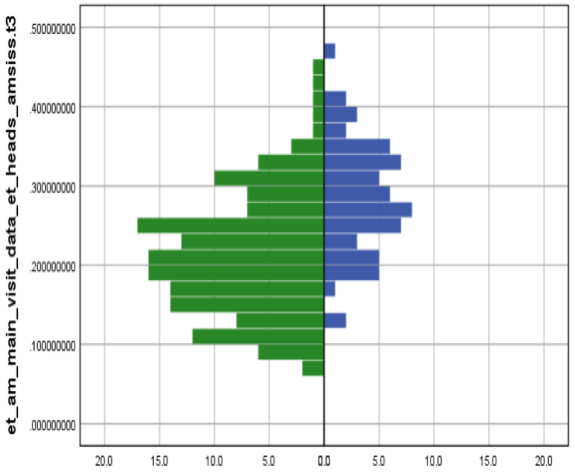
Frequency Frequency

ASD TD



Frequency Frequency

ASD TD &



Frequency Frequency &

Primary ET Biomarker: Oculomotor index

ICC	All	ASD	TD
T1,T2,T3	.83	.80	.78
T1,T2	.83	.79	.82
T1,T3	.83	.80	.77
T2,T3	.83	.81	.75